ABSTRACT

MoO_3

MOLYBDENUM TRIOXIDE

CAS No. 1313-27-5

Chemical Formula: MoO_3 Molecular Weight: 143.95

Synonyms: Molybdena; molybdenum anhydride; molybdenum (VI) oxide; molybdenum peroxide; molybdic acid anhydride; molybdic anhydride; molybdic oxide; molybdic trioxide; natural molybdite

Molybdenum is an essential element for the function of nitrogenase in plants and as a cofactor for enzymes including xanthine oxidoreductase, aldehyde oxidase, and sulfide oxidase in animals. Molybdenum trioxide is used primarily as an additive to steel and corrosion-resistant alloys. It is also used as a chemical intermediate for molybdenum products; an industrial catalyst; a pigment; a crop nutrient; components of glass, ceramics, and enamels; a flame retardant for polyester and polyvinyl chloride resins; and a reagent in chemical analyses. Molybdenum trioxide was nominated by the NCI for toxicity and carcinogenicity studies as a representative inorganic molybdenum compound. The production of molybdenum trioxide is the largest of all the molybdenum compounds examined.

Male and female F344/N rats and B6C3F$_1$ mice were exposed to molybdenum trioxide (approximately 99% pure) by inhalation for 14 days, 13 weeks, or 2 years. Genetic toxicology studies were conducted in *Salmonella typhimurium* and cultured Chinese hamster ovary cells.

14-DAY STUDY IN RATS

Groups of five male and five female F344/N rats were exposed to 0, 3, 10, 30, 100, or 300 mg molybdenum trioxide/m^3. Rats were exposed for 6 hours per day, 5 days per week, for a total of 10 exposure days during a 14-day period. All rats survived to the end of the study. The final mean body weights of male rats exposed to 100 mg/m^3 and male and female rats exposed to 300 mg/m^3 were significantly lower than those of the control groups. Male rats exposed to 300 mg/m^3 lost weight during the study. There were no clinical findings related to exposure to molybdenum trioxide. No chemical-related lesions were observed.

14-DAY STUDY IN MICE

Groups of five male and five female B6C3F$_1$ mice were exposed to 0, 3, 10, 30, 100 , or 300 mg molybdenum trioxide/m^3. Mice were exposed 6 hours per day, 5 days per week, for a total of 10 exposure days during a 14-day period. All mice survived to the end of the study. Final mean body weights of male and female mice exposed to 300 mg/m^3 were significantly lower than those of the control groups. Male mice exposed to 300 mg/m^3 lost weight during the study. There were no clinical findings related to exposure to molybdenum trioxide. No chemical-related lesions were observed.

13-WEEK STUDY IN RATS

Groups of 10 male and 10 female F344/N rats were exposed to molybdenum trioxide by inhalation at concentrations of 0, 1, 3, 10, 30, or 100 mg/m^3 for 6.5 hours per day, 5 days per week, for 13 weeks. All rats survived to the end of the study. The final mean body weights of exposed rats were similar to those of the control groups. No clinical findings related to molybdenum trioxide exposure were observed. There were no significant chemical-related differences in absolute or relative organ weights, hematology or clinical chemistry parameters, sperm counts or motility, or liver copper concentrations between control and exposed rats. No chemical-related lesions were observed.

13-WEEK STUDY IN MICE

Groups of 10 male and 10 female B6C3F$_1$ mice were exposed to molybdenum trioxide by inhalation at concentrations of 0, 1, 3, 10, 30, or 100 mg/m^3 for 6.5 hours per day, 5 days per week, for 13 weeks. All mice survived to the end of the study. The final mean body weights of exposed mice were similar to those of the control groups. There were no chemical-related clinical findings. There were no significant differences in absolute or relative organ weights or sperm counts or motility between control and exposed mice. There were significant increases in liver copper concentrations in female mice exposed to 30 mg/m^3 and in male and female mice exposed to 100 mg/m^3 compared to those of the control groups. No chemical-related lesions were observed.

2-YEAR STUDY IN RATS

Groups of 50 male and 50 female F344/N rats were exposed to molybdenum trioxide by inhalation at concentrations of 0, 10, 30, or 100 mg/m^3. Rats were exposed for 6 hours per day, 5 days per week, for 106 weeks.

Survival, Body Weights, and Special Studies

Survival rates of exposed male and female rats were similar to those of the control groups. Mean body weights of exposed groups of male and female rats were similar to those of the control groups throughout the study. There was a significant exposure-dependent increase in blood molybdenum concentration in exposed rats. Blood concentrations of molybdenum in exposed male rats were greater than those in exposed female rats. There were no toxicologically significant differences in bone density or curvature between control and exposed rats.

Pathology Findings

The incidences of alveolar/bronchiolar adenoma or carcinoma (combined) were increased in male rats with a marginally significant positive trend. No increase in the incidences of lung neoplasms occurred in female rats. Incidences of chronic alveolar inflammation in male and female rats exposed to 30 or 100 mg/m^3 were significantly greater than those in the control groups. No nasal or laryngeal neoplasms were attributed to exposure to molybdenum trioxide. Incidences of hyaline degeneration in the nasal respiratory epithelium in 30 and 100 mg/m^3 males and in all exposed groups of females were significantly greater than those in the control groups. The incidences of hyaline degeneration in the nasal olfactory epithelium of all exposed groups of females were significantly greater than that in the control group. In the larynx, incidences of squamous metaplasia of the epithelium lining the base of the epiglottis in all exposed groups of male and female rats were significantly greater than those in the control groups and increased with increasing exposure concentration.

2-YEAR STUDY IN MICE

Groups of 50 male and 50 female B6C3F$_1$ mice were exposed to molybdenum trioxide by inhalation at concentrations of 0, 10, 30, or 100 mg/m^3. Mice were exposed for 6 hours per day, 5 days per week, for 105 weeks.

Survival, Body Weights, and Special Studies

The survival rate of male mice exposed to 30 mg/m^3 was marginally lower than that of the control group; survival rates of 10 and 100 mg/m^3 males and of all exposed groups of females were similar to those of the control groups. Mean body weights of exposed male

mice were generally similar to those of the control group throughout the study. Mean body weights of exposed female mice were generally greater than those of the control group from week 11 until the end of the study. There was a significant exposure-dependent increase in blood molybdenum concentration in exposed mice. There were no toxicologically significant differences in bone density or curvature between control and exposed mice.

Pathology Findings

The incidences of alveolar/bronchiolar carcinoma in all exposed groups of males were significantly greater than that in the control group. Incidences of alveolar/bronchiolar adenoma in females in the 30 and 100 mg/m^3 groups were significantly greater than that in the control group. Incidences of alveolar/bronchiolar adenoma or carcinoma (combined) in 10 and 30 mg/m^3 males and in 100 mg/m^3 females were significantly greater than those in the control groups and exceeded the historical control ranges for 2-year NTP inhalation studies.

Incidences of metaplasia of the alveolar epithelium of minimal severity in the centriacinar region of the lung were significantly increased in all exposed groups of mice. The incidences of histiocyte cellular infiltration in all exposed groups of males were significantly greater than that in the control group. Incidences of hyaline degeneration of the respiratory epithelium of the nasal cavity in 100 mg/m^3 males and females and hyaline degeneration of the olfactory epithelium of the nasal cavity in 100 mg/m^3 females were significantly greater than those in the control groups. The incidences of squamous metaplasia of the epithelium lining the base of the epiglottis were significantly increased in all exposed groups of males and females. In both male and female mice, the incidences of hyperplasia of the laryngeal epithelium in level II of the larynx increased with increasing exposure concentration. The increase was statistically significant only in mice exposed to 100 mg/m^3 with 82% of male and 70% of female mice affected.

GENETIC TOXICOLOGY

Molybdenum trioxide was not mutagenic in any of five strains of *Salmonella typhimurium*, and it did not induce sister chromatid exchanges or chromosomal aberrations in cultured Chinese hamster ovary cells *in vitro*. All tests were conducted with and without S9 metabolic activation enzymes.

CONCLUSIONS

Under the conditions of these 2-year inhalation studies, there was *equivocal evidence of carcinogenic activity** of molybdenum trioxide in male F344/N rats based on a marginally significant positive trend of alveolar/bronchiolar adenoma or carcinoma (combined). There was *no evidence of carcinogenic activity* of molybdenum trioxide in female F344/N rats exposed to 10, 30, or 100 mg/m^3. There was *some evidence of carcinogenic activity* of molybdenum trioxide in male B6C3F$_1$ mice based on increased incidences of alveolar/bronchiolar carcinoma and adenoma or carcinoma (combined). There was *some evidence of carcinogenic activity* of molybdenum trioxide in female B6C3F$_1$ mice based on increased incidences of alveolar/bronchiolar adenoma and adenoma or carcinoma (combined).

Exposure of male and female rats to molybdenum trioxide by inhalation resulted in increased incidences of chronic alveolar inflammation, hyaline degeneration of the respiratory epithelium, hyaline degeneration of the olfactory epithelium (females), and squamous metaplasia of the epiglottis.

Exposure of male and female mice to molybdenum trioxide by inhalation resulted in increased incidences of metaplasia of the alveolar epithelium, histiocyte cellular infiltration (males), hyaline degeneration of the respiratory epithelium, hyaline degeneration of the olfactory epithelium (females), squamous metaplasia of the epiglottis, and hyperplasia of the larynx.

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* Explanation of Levels of Evidence of Carcinogenic Activity is on page 9. A summary of the Technical Reports Review Subcommittee comments and the public discussion on this Technical Report appears on page 11.

Summary of the 2-Year Carcinogenesis and Genetic Toxicology Studies of Molybdenum Trioxide

	Male F344/N Rats	Female F344/N Rats	Male $B6C3F_1$ Mice	Female $B6C3F_1$ Mice
Doses	0, 10, 30, or 100 mg/m^3	0, 10, 30, or 100 mg/m^3	0, 10, 30, or 100 mg/m^3	0, 10, 30, or 100 mg/m^3
Body weights	Exposed groups similar to control group	Exposed groups similar to control group	Exposed groups similar to control group	Exposed groups greater than control group
2-Year survival rates	17/50, 10/50, 16/50, 17/50	28/50, 24/50, 24/50, 23/50	36/50, 33/50, 25/50, 37/50	25/50, 31/50, 33/50, 35/50
Nonneoplastic effects	Lung: chronic inflammation, alveolus (2/50, 3/50, 25/50, 47/50) Nose: hyaline degeneration, respiratory epithelium (2/50, 7/49, 48/49, 49/50) Larynx: squamous metaplasia, epiglottis (0/49, 11/48, 16/49, 39/49)	Lung: chronic inflammation, alveolus (14/50, 13/50, 43/50, 49/50) Nose: hyaline degeneration, respiratory epithelium (1/48, 13/49, 50/50, 50/50); hyaline degeneration, olfactory epithelium (39/48, 47/49, 50/50, 50/50) Larynx: squamous metaplasia, epiglottis (0/49, 18/49, 29/49, 49/50)	Lung: metaplasia, alveolar epithelium (0/50, 32/50, 36/49, 49/50); histiocyte infiltration, cellular (2/50, 16/50, 9/49, 9/50) Nose: hyaline degeneration, respiratory epithelium (11/50, 13/50, 11/49, 41/50) Larynx: squamous metaplasia, epiglottis (0/50, 26/49, 37/48, 49/50); hyperplasia (1/50, 3/49, 6/48, 41/50)	Lung: metaplasia, alveolar epithelium (2/50, 26/50, 39/49, 46/49) Nose: hyaline degeneration, respiratory epithelium (26/49, 23/50, 28/49, 48/49); hyaline degeneration, olfactory epithelium (22/49, 14/50, 14/49, 36/49) Larynx: squamous metaplasia, epiglottis (1/49, 36/50, 43/49, 49/50); hyperplasia (1/49, 1/50, 7/49, 35/50)
Neoplastic effects	None	None	Lung: alveolar/ bronchiolar carcinoma (2/50, 16/50, 14/49, 10/50); alveolar/ bronchiolar adenoma or carcinoma (11/50, 27/50, 21/49, 18/50)	Lung: alveolar/ bronchiolar adenoma (1/50, 4/50, 8/49, 9/49); alveolar/bronchiolar adenoma or carcinoma (3/50, 6/50, 8/49, 15/49)
Uncertain findings	Lung: alveolar/ bronchiolar adenoma (0/50, 0/50, 0/50, 3/50); alveolar/bronchiolar carcinoma (0/50, 1/50, 1/50, 1/50); alveolar/ bronchiolar adenoma or carcinoma (0/50, 1/50, 1/50, 4/50)	None	None	None
Level of evidence of carcinogenic activity	Equivocal evidence	No evidence	Some evidence	Some evidence

Genetic toxicology

Salmonella typhimurium gene mutations:	Negative with and without S9 in strains TA97, TA98, TA100, TA1535, and TA1537
Sister chromatid exchanges Cultured Chinese hamster ovary cells *in vitro*:	Negative with and without S9
Chromosomal aberrations Cultured Chinese hamster ovary cells *in vitro*:	Negative with and without S9